

PRACA ORYGINALNA
ORIGINAL ARTICLE**DETERMINATION OF POOR OUTCOME PROGNOSIS
IN PATIENT WITH ACUTE LEUCEMIA WHICH WAS COMPLICATED
BY PNEUMONIA****CZYNNIKI RYZYKA ZŁEGO ROKOWANIA U PACJENTÓW Z OSTRĄ
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ABSTRACT

Introduction: At the present stage, the medicine development is based on the principles of evidence-based medicine, which requires using of statistical methods and forecasting. Using statistical analysis and possibilities and mathematical forecasting emphasizes the probability of obtained data in scientific medical research. Identifying the factors that determine the survival of patients with acute leukemia and pneumonia causes the conduct of this study.

The aim: To create a mathematical model of poor outcome prognosis in patients with acute leukemia, which was complicated by pneumonia, to determine the treatment place and timely optimize the treatment.

Materials and methods: An electronic database of formalized disease history of 360 patients with acute leukemia and pneumonia was created. The data base contained data of objective survey and additional research methods. In our study we used non-parametric dispersion analysis of Kraskale-Wallis, correlation analysis with the calculation of Spierman's rank correlation coefficients, simple and multiple logistic regression analysis with the calculation of the odds ratio; ROC analysis. The significance level $p < 0,05$ was considered statistically significant.

Results: It was determined that with the onset of the lethal outcome of patients with pneumonia, developed on the background of acute leukemia, the indicators of leukocytes, lymphocytes, neutrophils, platelets, erythrocytes, hemoglobin and immunity indexes (B(CD19+), T(CD4+), CD4+/CD8+, IgG). According to the results of our study, a mathematical model of prediction poor outcome in patients with acute leukemia, which was complicated by pneumonia, was created: $PPO = \exp(-10,317 + 0,410 * B(CD19+) - 2,149 * IgG) / [1 + \exp(-10,317 + 0,410 * B(CD19+) - 2,149 * IgG)]$.

Conclusion: Using in clinical practice the proposed mathematical model of prediction poor outcome in patients with acute leukemia, which was complicated by pneumonia, will allow determining the treatment place and timely optimizing the treatment program.

KEY WORDS: acute leukemia, prognosis, pneumonia, poor outcome

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INTRODUCTION

According to the International Agency for Research on Cancer (Lyon, France), more than 10 million patients with malignant neoplasms were registered in the world in 2000, and the number of new cases is projected to reach 16 million in 2020 [1]. The problem of leukemia is one of the most urgent. Leukemia is about 8% of the total number of malignant tumors, and are among the six most common cancers. Every 3 minutes a new case of cancer is registered in the USA, and every 9 minutes one of the patients dies [2]. Up to 8 thousand new cases of oncohematological diseases are diagnosed annually in Ukraine. The index of morbidity per 100 thousand population at lymphogranulomatosis is 2,5; at MM – 1,6; at leukemia – 8,1 [3]. According to official data, the incidence of hemoblastosis in Ukraine during the last 20 years has increased from 14,7 (in 1991) to 18,9 per 100 thousand population (2014). The absolute number of newly diagnosed patients also increased [4, 5, 6]. The end of oncohematological diseases is often unfavorable. Timely

diagnosis provides 2/3 of success in overcoming illness. The situation with the treatment of acute leukemia in adults remains unsatisfactory. The frequency of remissions abroad – 50–80%, in Ukraine it does not exceed 20–40% [7]. The using of integrated therapies allowed prolong the patients' lives with AL in remission, up to 3–5 years in 35–40% of cases and to remove the terms of patients' disability with chronic blood and lymphoid tissue diseases [8]. At the same time, the survival prognosis of patients with AL became worst with infectious complications (IC), among them the leading role belongs to pneumonia [8]. It is proved that the course of AL is characterized by a high incidence of IC, which pneumonia is the main one. It occurs in 53% of hospitalized in the hematological department [9]. Mortality in such cases is quite high and makes up 28% [8]. Progressive increase of pneumonia poor outcome is determined even modern antibacterial drugs using. The mortality level of patients with AL and pneumonia reaches to 40% in the intensive care units [10].

Table I. Odds ratio clinical and laboratory parameters influence on mortality, depending on their threshold predictive value of the studied patients

Indexes (1 – yes, 0 – no)	OR	95% CI	Patients proportion, (%)		p
			Alive	Dead	
Neutrophils $\leq 1,24 \cdot 10^9/l$	10,20	5,52 - 18,83	7,05	43,61	<0,001
Pulse >92 per min.	17,31	9,90 - 30,26	10,57	67,18	<0,001
Leukocytes $\leq 3,7 \cdot 10^9/l$	60,00	7,60 - 473,85	28,57	96,0 %	<0,001
Lymphocytes $\leq 18,9$ %	9,90	4,51 - 21,76	18,75	69,57	<0,001
B CD19 $\leq 0,467$ g/l	68,85	4,0 - 1185,95	37,14	100,0	<0,001
T CD19+ $>58,13$ %	85,79	18,06 - 407,47	14,46	93,55	<0,001
CD4 $\leq 21,77$ %	285,0	32,41 - 2506,38	78,4	21,6	<0,001
CD4 $\leq 0,71$ g/l	28,80	6,14 - 134,98	6,25	95,0	<0,001
CD4/CD8 $\leq 1,05$	437,0	46,23 - 4130,90	4,17	95,0	<0,001
Ig G $\leq 8,21$ g/l	43,54	5,51 - 344,13	30,38	95,0	<0,001
FA $\leq 22\%$	14,44	4,19 - 49,75	8,70	57,89	<0,001
Creatinine >94 mkmol/l	3,84	2,44 - 6,03	32,30	64,66	<0,001
HB ≤ 90 g/l	6,02	3,72 - 9,73	33,48	75,19	<0,001
Erythrocytes $\leq 1,97 \cdot 10^{12}/l$	36,67	19,21 - 70,00	6,61	72,18	<0,001
ESR >33 mm/h	4,63	2,92 - 7,34	31,86	68,42	<0,001
Platelets $\leq 60 \cdot 10^9/l$	8,50	5,15 - 14,03	15,49	60,90	<0,001

At the present stage, the medicine development is based on the principles of evidence-based medicine, which requires using of statistical methods and forecasting. Using statistical analysis and possibilities and mathematical forecasting emphasizes the probability of obtained data in scientific medical research. Identifying the factors that determine the survival of patients with AL and pneumonia causes the conduct of this study.

THE AIM

To create a mathematical model for determine the forecast of pneumonia poor outcome in patients with acute leukemia in order to define patient's treatment place and timely optimize the treatment.

MATERIALS AND METHODS

The study was conducted in the hematological center of "City Multidisciplinary Clinical Hospital №4", Dnipro (2012–2015 yrs). 360 patients with pneumonia developed on a background of AL were investigated. The patients were divided according to the American Thoracic Society recommendations 2007 [15]: the 1st group consisted of 109 patients with mild and moderate severity of pneumonia, which developed shortly after hospitalization; the 2nd group consisted of 65 patients with mild and moderate severity of pneumonia, which developed at any time, all patients have risk factors; the 3rd group – 53 patients with severe pneumonia, which developed shortly after hospitalization, all patients have risk factors and patients with late pneumonia with severe course. In addition, we identified 4th group – patients with pneumonia poor outcome. This

group consisted of 133 patients.

Diagnosis of pneumonia and CL form were performed in accordance with generally accepted clinical, laboratory and morpho-immunohistochemical studies [1, 2, 7, 8, 9, 17].

General clinical methods included data of anamnesis, including anamnesis of oncohematological disease (form, stage of the disease, its first signs, duration, presence of B-symptoms, enlargement of liver, spleen, lymph nodes (LV), number of chemotherapy courses (CT), which preceded the IC of the broncho-pulmonary system, the presence of concomitant pathology, anamnesis of pneumonia (communiyu aquared pneumonia, nosocomial pneumonia (early, late)); the beginning, the presence of generally accepted clinical signs; data of pneumonia clinical picture and complaints (the presence, number and nature of sputum, the presence, number and type of dyspnea, the time when complaints began, temperature reaction dynamics); data of patient's physical examination, including in dynamics (data of percussion, auscultation); results of laboratory methods of research in dynamics (complete blood count, biochemical blood test); general sputum analysis; chest X-Ray in two projections and / or computed tomography (CT) of the lungs (if necessary in dynamics); to determine the probable pathogens of pneumonia – bacterioscopic and microbiological study of sputum and fluid of broncho-alveolar lavage (BAL); fibrobronchoscopy to obtain BAL fluid; immuno-enzymes study - to determine the parameters of cellular and humoral immunity.

All quantitative and qualitative (nominal) indices were entered into the electronic database of formalized disease histories like "object-sign" table. These data gradually and statistically processed using descriptive and analytical biostatistics methods implemented in software packages

Table II. Forecast of pneumonia poor outcome in patients AL according to logistic regression analysis

Prognostic Variables	Regression coefficient β	Standard error of coefficient β	Wald's χ^2	Wald's p-value χ^2
Free member of the equation	-10,317			
T CD19+ % (x_1)	0,410	0,162	6,429	0,011
Ig G (x_2)	-2,149	0,944	5,189	0,023
Logistic equation	$y = \exp(-10,317 + 0,410 \cdot x_1 - 2,149 \cdot x_2) / [1 + \exp(-10,317 + 0,410 \cdot x_1 - 2,149 \cdot x_2)]$			
Xi- square	$\chi^2 = 65,37$ ($p < 0,001$)			
Percentage of concordance	93,67 %			
Hosmer-Lemeshov Test	0,127 ($p = 0,999$)			
Forecasting operating characteristics according to ROC analysis				
Sensitivity, %	100,0			
Specificity, %	90,48			
AUC	0,991			
95 % CI AUC	0,938 - 1,000			
p	<0,001			
Qualitative assessment of the model	excellent			

“STATISTICA 6.1” (StatSoftInc., Serial No. AGAR909E-415822FA); Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT). Median (Me), as a measure of the central trend, was used to describe the quantitative indices; interquartile scale ((25%, 75%) – 25 and 75 percentiles respectively, Q1 and Q3 – first and third quartiles) to describe the sings variation., The nonparametric dispersion analysis of Kraskale-Wallis and a correlation analysis with the calculation of the Spirman rank correlation coefficients (ρ) were used in statistical analysis of study results. Multiple comparisons were made with Bonferon and Hill. The statistically significant level was $p < 0,05$ (5%) [10].

RESULTS

Correlation between mortality and clinical, anamnestic, laboratory parameters shows the existence of probable connection between poor outcome forecast and 36 quantitative and qualitative sings.

The indicators with statistically significant, average and high correlation coefficients ($0,29 < \rho < 1,0$) were selected for a more detailed analysis of which factors affect on poor outcome. The next step was - to analyze the effect of quantitative and nominal indicators on the mortality of patients with pneumonia and AL using a simple logistic regression analysis. Cutoff points were identified using the ROC analysis – the critical values of the clinical and laboratory results, which achieved the maximum predictive value of the indicator to predict the probability of pneumonia poor outcome [18].

Leukocytes, lymphocytes, neutrophils, platelets, erythrocytes, hemoglobin, B (CD19 +) (g / l), CD4 + (%), immunoregulatory index (CD4 + / CD8 +) and IgG (g / l)

showed the most prognostic ability to predict pneumonia lethal outcome in patients with AL (Tab. I).

The relationship between the signs “died” or “survived” analyzed using a logistic regression model with a step-by-step algorithm predictors inclusion [13, 14]. The logistic equation used as the basis for developing the prediction model: $y = \exp(b_0 + b_1 \cdot x_1 + \dots + b_n \cdot x_n) / [1 + \exp(b_0 + b_1 \cdot x_1 + \dots + b_n \cdot x_n)]^{(1)}$, where: y – the result (in our study – the prediction of pneumonia poor outcome (PPO); b_0 – the free part of the regression equation; b_1 – b_n - regression coefficients; x_1 - x_n – predictor variables.

If the calculated probability of pneumonia poor outcome will be less than 0,5, we can assume that the event will not occur (the patient will not die); if probability more than 0,5 – the poor outcome of pneumonia is reliable.

We received the logistic regression equation parameters represented as a result of a step-by-step inclusion of independent variables. It's presented in tab. II (only meaningful factors are included in the table). For quantitative predictors, the index entered in the equation in units values, for binary 1 – factor is presented, 0 – is not.

We calculated the regression coefficient β during logistic regression analysis, its error, and χ^2 Wald statistics. Coefficient β describes the change of the mortality risk due to risk factor change for the one unit. We estimated the predictive precision of the logistic regression equation using the Hi-square (χ^2); percentage of concordant - the proportion of correctly reclassified observations (the closer this figure to 100%, the higher model quality); Hosmer-Lemeshov's consent test and ROC-analysis. The evaluation of logistic regression equations using Xi-square (χ^2) showed their precision, it was determined the statistically significant level χ^2 ($p < 0,001$). The proportion of correct prediction for patients with AL membership of a particular group

(survivor, died) was 93,67%. This concordance indicator shows a high degree of consistency in the real distribution of mortalities and distribution based on the logistic regression equation. Overall consensus actual and estimated data based on Hosmer- Lemeshov test showed significant match, because $p > 0,05$ was for all equations. That allows us to take zero hypothesis regarding the consistency of the theoretical and actual results of the disease.

According to the ROC curve's shape and the area under it (AUC), we estimated the predictive precision of logistic regression equations. The area under the ROC curve shows the dependence between the numbers of correctly and incorrectly classified pneumonia poor outcome cases. The closer curve to the upper left corner and the bigger the area under the curve, the better its discriminatory power. When the AUC is 0.9 - 1, the model's quality is considered "excellent"; 0,8 - 0,9 - "very good"; 0,7 - 0,8 - "good"; 0,6 - 0,7 - "average"; 0,5 - 0,6 - "unsatisfactory"; the value less than 0,5 indicates the model's unsuitable [18,19].

Thus, it is determined that the proposed prognostic model - the logistic regression equation has excellent operational characteristics - sensitivity 100,0%, specificity 90,48%, area under the ROC curve - 0,991 ($p < 0.001$) (Table II, Fig. 1).

The constructed logistic models were acceptable relying on the criterion χ^2 ; the percentage of concordation, the Hosmer-Lemeshov test and the ROC-analysis. The predicted values (y) in regression models will be always in ranges from 0 (survived) to 1 (died), regardless of regression coefficients or x -values. When calculated probability is less than 0,5, we can supposed that event will not occur (the patient will not die); otherwise (probability more than 0,5) - the pneumonia poor outcome will be [19].

We propose a detailed scale for predicting the pneumonia poor outcome (PPO) in patients with AL based on all of the above calculations:

- up to 0,21 - very low probability of PPO ($P < 5,24\%$);
- 0,22 - 0,42 - low probability of PPO ($5,24\% \leq R < 25,08\%$);
- 0,43 - 0,55 - average probability of PPO ($25,08\% \leq R < 50,50\%$);
- 0,56 - 0,81 - high probability of PPO ($50,50\% \leq R \leq 90,45\%$);
- higher than 0.82 - very high probability of PPO ($P > 90,45\%$).

DISCUSSION

Despite the presence of a sufficiently large number of prognostic and diagnostic scales, which are certainly useful for a physician, which solves the issue of choosing the treatment place, diagnosis, the severity of pneumonia, we can't consider this issue to be finally resolved, especially for certain categories of patients, in particular for patients with AL and pneumonia. Earlier the determination of the forecast mortality based on the analysis of leading symptoms and syndromes, but at present time it is possible to use the mathematical apparatus [17]. Quantitative analysis provides an opportunity to determine prognostic evaluation

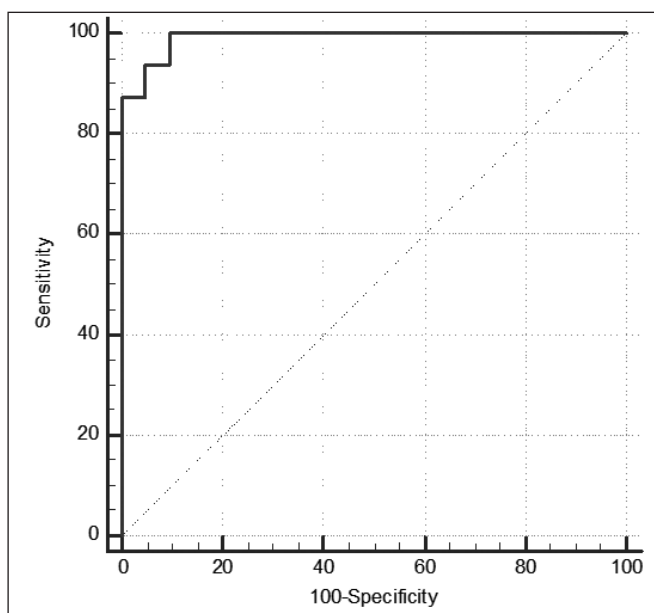


Fig.1. Operational characteristics of the forecasting pneumonia poor outcome logistic regression model in patients with AL according to ROC analysis.

criteria in numerical terms enriching and supporting the meaningful analysis, making it more evidence, excluding contradictory methods [17].

The study identified the factors predicting pneumonia poor outcome in patients with pneumonia, developed on the background of AL. The study proved that the predictors of the poor outcome were: leukocytes, lymphocytes, neutrophils, platelets, erythrocytes, hemoglobin, as well as immunity parameters: B (CD19 +) (G / L), CD4 + (%), immunoregulatory index (CD4 + / CD8 +) and IgG (g / l). The logistical equation included two of the most influential indicators - B CD19 + (G / L) and IgG (g / l). It is known that the main effector cells-killers are T-lymphocytes. They provide recognition and destruction of cells that carry external antigens, in particular infectious agents [20]. The number of these cells is usually lowered in patients with acute leukemia. The function of B-lymphocytes with the phenotype B (CD19 +) is the formation of complexes with antigenic receptors of B-lymphocytes and a decrease in the threshold of sensitivity of these receptors that stimulate the functional activity of T-killers [20]. Also, this phenotype, in terms of its quantitative reduction, characterizes the redistribution of lymphocytes to the inflammatory site. Therefore, it is clear that the quantitative decrease of B (CD19 +) is defined as a predictor of the poor outcome of such a severe IC, as pneumonia in patients with AL. The obtained data coincide with the data of other researchers, which determined the role of the indicator B (CD19 +) for its increase - as a sign of a favorable forecast; for a decrease - as a sign of an unfavorable prognosis in patients with MM [21].

Using in clinical practice the obtained equation will allow to predict the pneumonia poor outcome in patient with chronic leukemia with a small number of parameters that

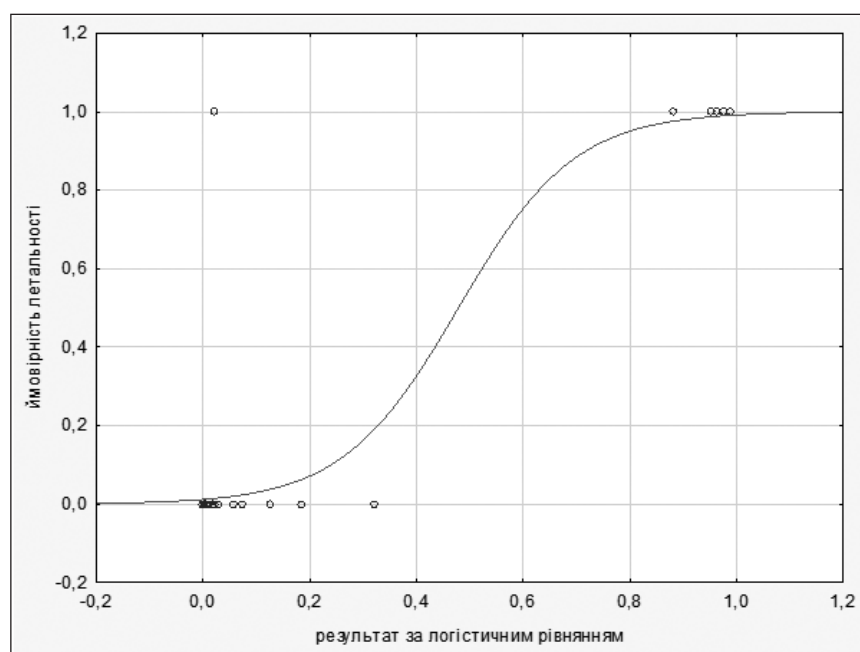


Fig. 2. Dependence on calculated logistic equation result the probability of pneumonia poor outcome in patient with acute leukemia.

are available today in clinics with hematological profile. Determination the probability of PPO in patients with AL has a fundamental value for timely choice the treatment tactics:

- 0,21 – 0,42 – low probability of PPO – it is possible to treat pneumonia in outpatient settings or in a therapy, hematologist consultation is necessary;
- 0,43 – 0,55 – average probability of PPO – treatment in therapy, hematologist consultation in dynamics of treatment;
- 0,56 – 0,81 – high probability of PPO – treatment in a hematological hospital, determination of immunity parameters in dynamics, consideration necessity of ABT modification;
- more than 0,82 – very high probability of PPO – treatment in the department of intensive care, optimization of ABT.

CONCLUSIONS

1. Results of our study prove that the forecast of pneumonia poor outcome in patients with acute leukemia is associated with: leukocytes, lymphocytes, neutrophils, platelets, erythrocytes, hemoglobin and immunity: B (CD19+) (G/L), T (CD4+) (%), immunoregulatory index (CD4+/CD8+) and IgG (g/l).
2. Mathematical modeling is a modern, necessary instrument in medical practice. A mathematical model for predicting the pneumonia poor outcome in patients with acute leukemia was created in our study: $PPO = \exp(-0.073 - 0.994 * (\text{leukocytes}) + 4.842 * (P. \text{aeruginosa})) / [1 + \exp(-0.073 - 0.994 * (\text{leukocytes}) + 4.842 * (R. \text{aeruginosa}))]$.
3. Using in clinical practice the proposed mathematical model of prediction pneumonia poor outcome in patients with acute leukemia will allow determining the treatment place and timely optimizing the treatment program. If the result of equality is 0,21 – 0,42 – it is

possible to treat pneumonia in outpatient settings or in a therapy, hematologist consultation is necessary; 0,43 – 0,55 – treatment in therapy, hematologist consultation in dynamics of treatment; 0,56 – 0,81 – treatment in a hematological hospital, determination of immunity parameters in dynamics, consideration necessity of ABT modification; if result more than 0,82 – treatment in the department of intensive care, optimization of ABT.

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Authors' contributions:

According to the order of the Authorship.

Conflict of interest:

The Authors declare no conflict of interest.

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